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10/018,878	03/06/2002	David MARTIN Anderson	PX3813USW	8728

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EXAMINER

RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary**Application No.**

10/018,878

Applicant(s)

ANDERSON ET AL.

Examiner

Delia M. Ramirez

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 7/3/2203.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5-8,10-15,21,24,25,29-37,40,41,43-46,48 and 49 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1,2,5,6,11-14,29,30 and 32 is/are allowed.
- 6) ☒ Claim(s) 7,24,25,31,40,41,43,44,49 is/are rejected.
- 7) ☒ Claim(s) 8,10,15,21,33-36,45-46,48 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Status of the Application

Claims 1-2, 5-8, 10-15, 21, 24-25, 29-37, 40-41, 43-46, 48-49 are pending.

Amendment of claims 1-2, 5-8, 10, 14, 15, 21, 24-25, 29-37, 40-41, 43-44, cancellation of claims 3-4, 9, 16-20, 22-23, 26-28, 38-39, 42, 47, and addition of claim 49, in a communication filed on 7/3/2003, is acknowledged.

The Examiner contacted Mr. Michael Conger on 11/21/03 to discuss amendments to the claims which would have placed the application in condition for allowance but no agreement could be reached.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Terminal Disclaimer

1. The terminal disclaimer filed on 7/3/2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on Application Number 09/345492 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Specification

2. The disclosure remains objected to since the trademarks recited have not been capitalized. See specifically pages 14-28 of the specification as indicated in the previous Office Action mailed on 3/11/2003. Appropriate correction is required.

Drawings

3. The formal drawings submitted on 7/3/2003 are accepted by the Examiner.

Claim Objections

4. Claim 8 (claim 10 dependent thereon) is objected to due to the recitation of “wherein the transcriptional unit comprises the modified T4 nrdA gene and the nrdB gene” as it is redundant. Claim 8 is dependent upon claim 7, which already contains the limitation in regard to the T4 nrdA gene and the T4 nrdB gene. For clarity, it is suggested that the term be deleted. Appropriate correction is required.
5. Claim 15 is objected due to the recitation of “such that ribonucleotide”. For clarity, the term “such that ribonucleotide” should be replaced with “such that the ribonucleotide”. Appropriate correction is required.
6. Claim 15 is objected to due to the recitation of “wild type equivalent of said ribonucleotide reductase encoded by the unit comprising an unmodified nrdA gene” as it is redundant. For clarity, it is suggested that the term be amended to recite “wild type equivalent of said ribonucleotide reductase”. Appropriate correction is required.
7. Claim 21 is objected to due to the recitation of “T4 td gene”. While it is understood that “td” is gene nomenclature, for clarity, it is suggested that the term be amended to recite “T4 td (thymidylate synthase) gene”. Appropriate correction is required.
8. Claim 25 is objected to due to the recitation of “wherein td gene”. For clarity, it is suggested that the term be replaced with “wherein the td gene”. Appropriate correction is required.
9. Claim 31 is objected to due to the recitation of “3, 4, 9, 16-20..”. This appears to be a typographical error. Appropriate correction is required.
10. Claim 33 (claims 34, 35, 37, 45, 46, 48 dependent thereon) is objected to due to the recitation of “1, 2, 5-8, 10-15, 21, 24, 25, 29-32”. The list of claims recited should be in the alternative form. It is suggested that the term be amended to recite “1, 2, 5-8, 10-15, 21, 24, 25, or 29-32”. Appropriate correction is required.

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11. Claim 36 is objected to due to the recitation of “polynucleotides comprises”. It should be replaced with “polynucleotide comprises”. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 7, 24-25, 31, 40, 41, 43 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claim 7 is indefinite in the recitation of “DNA construct according to claim 6 wherein the vector is a plasmid” since there is no antecedent basis for the plasmid. It is suggested that the claim be amended to recite “DNA construct according to claim 5” instead. Correction is required.

15. Claim 24 (claim 25 dependent thereon) is indefinite in the recitation of “DNA construct according to claim 21 wherein the td gene is located in the same operon as the nrdA, nrdB, and nrdC genes” as there is no antecedent basis for the operon, the nrdA, nrdB or the nrdC genes. It is suggested that claim 21, from which claim 24 depends upon, be amended to recite “A DNA construct according to claim 7 wherein the construct further comprises the T4 td (thymidylate synthase) gene”. Correction is required.

16. Claim 31 is indefinite in the recitation of “DNA construct according to claim 1 wherein the E. coli uridine kinase gene..” since there is no antecedent basis for the E. coli uridine kinase gene. It is suggested that the claim be amended to recite “DNA construct according to claim 30 wherein the E. coli uridine kinase gene..”. Correction is required.

17. Claim 40 (claims 41, 43, 44 dependent thereon) is indefinite in the recitation of “construct comprises a transcription DNA unit, which unit comprises a modified T4 nrdA gene modified T4 nrdA gene comprising SEQ ID NO: 9 and a T4 nrdB gene encoding a ribonucleotide reductase and a T4 nrdC

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gene, wherein said ribonucleotide reductase displays less.....” for the following reasons. First, there is no antecedent basis for a “transcription DNA unit”. In addition, the term “a modified T4 nrdA gene modified T4 nrdA gene comprising SEQ ID NO: 9” appears to have a typographical error. Furthermore, while the specification discloses that the ribonucleotide reductase which exhibits less allosteric inhibition is the product of the modified T4 nrdA gene, the claim as written appears to recite that the T4 nrdB gene encodes the ribonucleotide reductase which displays less allosteric inhibition. It is suggested that the claim be amended to recite “construct comprises a transcription unit, which unit comprises a modified T4 *nrdA* gene comprising SEQ ID NO: 9, a T4 *nrdB* gene, and a T4 *nrdC* gene, wherein the modified T4 *nrdA* gene encodes a ribonucleotide reductase which is less sensitive to allosteric inhibition than the wild-type equivalent of the reductase, and wherein said host cell further comprises one or more of the following ...”. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claim 49 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

20. Applicants submit that the invention is properly described and that the scope of Applicant’s claims should not be limited to a particular example of modification given in the specification.

21. Applicant’s arguments are not deemed persuasive to avoid the rejection of newly added claim 49 for the following reasons. Claim 49 is directed to a genus of DNA constructs comprising the T4 nrdA

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gene wherein said gene has been modified in any way within the region encoding the dTTP binding site such that the ribonucleotide reductase encoded by said gene is less sensitive to allosteric inhibition than the wild type equivalent of said reductase. While the specification discloses a T4 nrdA gene mutant wherein the ribonucleotide reductase A (encoded by the nrdA gene) is less sensitive to allosteric inhibition than the wild type T4 ribonucleotide reductase A due to an Ala to Ile amino acid substitution at position 79 of the T4 ribonucleotide reductase A, the specification is silent in regard to other modifications in the dTTP binding site of the T4 nrdA gene product which would result in a ribonucleotide reductase which is less sensitive to allosteric inhibition. The specification fails to disclose (1) the amino acid residues which are part of the dTTP binding site, (2) which amino acids in the dTTP binding site of the T4 ribonucleotide reductase A are most likely to be associated with allosteric inhibition, (3) which amino acids can be used to substitute those in the dTTP binding site most likely to be associated with allosteric inhibition, and (4) which modifications, i.e. insertions, deletions or substitutions, in the dTTP binding site are more likely to result in a reduction of allosteric inhibition with the exception of the Ala to Ile substitution at position 79. The specification only discloses a single species of the claimed genus which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the claimed genus. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

22. Claim 49 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a T4 nrdA gene which has been mutated such that there is an Ala to Ile amino acid substitution at position 79 in the T4 ribonucleotide reductase A product encoded by such gene, does not reasonably provide enablement for a DNA construct comprising the T4 nrdA gene wherein said gene has been modified in any way within the region encoding the dTTP binding site such that the ribonucleotide

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reductase encoded by said gene is less sensitive to allosteric inhibition than the wild type equivalent of said reductase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

23. Applicants submit that the invention is enabled and that the scope of Applicant's claims should not be limited to a particular example of modification given in the specification. According to Applicants, the specification gives one of skill in the art sufficient guidance as to how other useful modifications could be determined and employed without undue experimentation.

24. Applicant's arguments are not deemed persuasive to avoid the rejection of newly added claim 49 for the following reasons. The scope of the claim, as described above, is not commensurate with the enablement provided in regard to the potentially large number of unknown modifications in the T4 *nrda* gene encompassed by the claim. As indicated above, there is no information as to which amino acid residues constitute the T4 ribonucleotide reductase A dTTP binding site, which of the amino acids in the dTTP binding site are associated with allosteric inhibition, which amino acids can be used to substitute those in the dTTP binding site which are associated with allosteric inhibition such that a mutant with less allosteric inhibition is obtained, or which modifications, i.e. deletions, insertions, or substitutions in the dTTP binding site are more likely to result in less allosteric inhibition with the exception of the Ala to Ile substitution at position 79. As indicated in the previous Office Action mailed on 3/11/2003, the state of the art teaches how small structural changes can result in major changes in function. See particularly the teachings of Broun et al. (Science 282:1315-1317, 1998) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) previously discussed. Since structure determines function, one of skill in the art would require some knowledge or guidance as to which are the structural elements (i.e. residues) that constitute the dTTP binding site, which of those elements in the dTTP binding site are associated with allosteric inhibition, and which substitutions can be made in those residues associated with allosteric inhibition such

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that one of skill in the art can create mutants of the T4 ndrA gene which encode a ribonucleotide reductase with less allosteric inhibition than the wild-type counterpart.

Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements associated with allosteric inhibition or the dTTP binding site, and the unpredictability of the prior art in regard to how structural changes can result in major functional changes, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to (1) determine which structural elements constitute the dTTP binding site in the T4 nrdA gene product (2) determine which of these structural elements in the dTTP binding site are associated with allosteric inhibition, (3) which amino acids should be used to substitute those in the dTTP binding site which are associated with allosteric inhibition, and (4) which modifications, in addition to the single one disclosed in the specification, are more likely to result in less allosteric inhibition. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

25. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

26. Claims 1, 5-6, 11, 12, 32, 33, 45-46 were rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. (J. Bacteriol. 174(17):5647-5653, 1992). Wang et al. teaches cloning and expression of E. coli dCTP deaminase (dcd gene).

27. Since Wang et al. teaches cloning and expression of the E. coli dCTP deaminase (dcd gene) and the claims are now directed to (1) a DNA construct comprising a T4 nrdA gene comprising SEQ ID NO: 9, a T4 nrdB gene and a T4 nrdC gene, (2) a DNA construct as in (1) further comprising the E. coli dcd

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gene, a host cell comprising (1) or (2), and (3) a process to produce pyrimidine deoxyribonucleosides with the host cells of (2), this rejection is hereby withdrawn.

Claim Rejections - 35 USC § 103

28. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

29. Claim 13 was rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (J. Bacteriol. 174(17):5647-5653, 1992) in view of Lim et al. (Biotechnol. Prog. 14:548-553, 1998).

30. Claim 13 is dependent upon claim 1. In view of the fact that claim 1 is no longer anticipated by Wang et al. for the reasons set forth above, and since neither Wang et al. or Lim et al. teach the invention of claim 13 alone or in combination, this rejection is hereby withdrawn.

Double Patenting

31. Claims 1-2, 5-8, 10-15, 21, 24-25, 29-37, 40-41, 43-44 and 48 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12, 14-17, 29-38, 44-46, 50-61 of copending Application No. 09/345,492.

32. Submission of a terminal disclaimer filed on 7/3/2003 is deemed sufficient to overcome the previous double patenting rejection applied to claims 1-2, 5-8, 10-15, 21, 24-25, 29-37, 40-41, 43-44 and 48. Thus, this rejection is hereby withdrawn.

Allowable Subject Matter

33. Claims 1-2, 5-8, 10-15, 21, 24-25, 29-37, 40-41, 43-46, and 48 appear to be allowable over the prior art of record. Claims 7-8, 10, 15, 21, 24-25, 31, 33-36, 40-41, 43-44, 45-46, and 48 would be

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allowable if rewritten to overcome the objections and/or 35 USC 112, second paragraph as discussed above.

Conclusion

34. Applicant's amendment of claims 1-2, 5-8, 10, 14, 15, 21, 24-25, 29-37, 40-41, 43-44 and addition of new claim 49 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

35. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or

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relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


Delia M. Ramirez, Ph.D.

Patent Examiner

Art Unit 1652

DR

November 24, 2003


REBECCA E. PROUTY
PATENT EXAMINER
1652